Kathleen:
I have reviewed the FDA proposed draft regarding (3789)

1. Page 2, para IV Clinical Studies: the t score should be greater than 2.5 not less than. This is always confusing with a negative number but it needs to indicate T scores such at -3, -4 or -5.

1697 '00 SEP 20 A9:22

2. Page 2, para IV: Radiographically documented should be expanded to indicate documented by radiologic techniques, such as x-ray, MRI, CT, Bone scan or Dexa scan.

3. Patient follow up: These should be some guidelines on how to notice osteosarcomas in these patients-e.g. perioidic bone scans.

4. Clinical Studies: Should only patients with a single cause of osteoporosis, such as postmenopausal disease, be studied. This would make the most sense to me so that other causes of osteoporosis, such as vit D deficiency or hyperthyroidism, which may be more problematic with regard to risk for osteosarcoma, would be excluded.

Thanks
Ken

KB

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000-1307

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**Kenneth D. Burman, MD**
*Director, Section of Endocrinology*

[redacted] FDA Action
[redacted] 08-24 14:25:10 EDT
From: REEDYK@cder.fda.gov (Kathleen Reedy 301-827-7001 FAX 301-827-6776)
To: robert.sherwin@yale.edu, cws@u.washington.edu, bisaccip@ohsu.edu, hirsch@rockvax.rockefeller.edu, molitch@northwestern.edu, rkreisberg@usamail.usouthal.edu, endodiab@altinet.net, jcara1@aol.com, marcuse@leland.stanford.edu, rhinew@mail.med.cornell.edu, hgbone.md@worldnet.att.net, braunstein@cshs.org, colley.colleen_A@portland.va.gov, rkcamp@wsu.edu, bears21@aol.com, oppen001@maroon.tc.umn.edu, madavids@cdrewu.edu, silvejh@peds.ufl.edu, smg15@po.cwru.edu, dporte@ucsd.edu, blukert@kumc.edu, llevitsky@partners.org, cleary@biostat.bsc.gwu.edu, mgelato@notes.cc.sunysb.edu, dgrady@itsa.ucsf.edu, asampson@stat.pitt.edu, william.tamborlane@yale.edu, ttaoki@ucdavis.edu, rwkillion@hhlaw.com



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FDA Approves First NDA for Levothyroxine Sodium

On August 22, 2000, the FDA approved the first NDA for the thyroid hormone replacement drug, levothyroxine sodium (Unithroid) for use in adults and children. Levothyroxine is identical to a natural thyroid hormone produced by the body and is most commonly used to return thyroid hormone levels to normal in patients with hypothyroidism. The dose of levothyroxine for replacement or supplemental therapy in patients with hypothyroidism must be individualized based on patient response. Patients taking levothyroxine as replacement must be monitored with blood tests at regular intervals to determine that thyroid hormone levels are within the normal range, to assure patient safety, and to help guide dose adjustments. Side effects from levothyroxine are usually due to over-dosage and include nervousness, weight loss, tachycardia (rapid heart beat), irritability, and anxiety. Unithroid is manufactured and distributed by Jerome Stevens Pharmaceuticals of Bohemia, NY.

For additional information, visit the FDA's "What's New" website at http://www.fda.gov/opacom/hpwhats.html.

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---------- Headers ----------
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via smtpd (for rly-za01.mx.aol.com [152.163.224.1]) with SMTP; 24 Aug 2000 18:21:02 UT
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WorldSecure Server SMTP Relay(WSS) v4.3); Thu, 24 Aug 00 14:25:20 -0400
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Date: Thu, 24 Aug 2000 14:24:48 -0400 (EDT)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

**5630 Fishers Lane, Rm. 1093**
**Advisors & Consultants Staff HFD-21**
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**Date: September 6, 2000**

**From:** Kathleen R. Reedy, Executive Secretary
Endocrinologic and Metabolic Drugs Advisory Committee

**To: Advisory Committee Members and Consultants**

**Subject:** **Guidance for Industry:**
**Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis**

**The Division of Metabolic and Endocrine Drug Products has issued a draft guidance document for which we are inviting comment. We hope that you, our advisors and consultants will submit comment.**

**Enclosed you will find:**

Federal Register notice containing background information and specific directions and addresses for submitting comment.

The Draft Guidance

You are welcome to send a copy of your submission to me also.

Kathleen

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. 00D-1307]

### Draft Guidance for Industry on Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis; Availability

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis." Parathyroid hormone (PTH) is being studied for use in the prevention and treatment of osteoporosis. In response to preclinical studies submitted to FDA in which osteosarcomas developed in rats and mice following administration of PTH and related peptides, the agency is developing guidance for the development of PTH as a drug for osteoporosis. This guidance is intended to improve the benefit to risk ratio of treatment with PTH and related peptides.

**DATES:** Submit written comments on the draft guidance by August 14, 2000. General comments on agency guidance documents are welcome at any time.

**ADDRESSES:** Copies of this draft guidance for industry are available on the Internet at http://www.fda.gov/cder/guidance/index.htm. Submit written requests for single copies of the draft guidance to the Drug Information Branch (HFD-210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Eric Colman, Center for Drug Evaluation and Research (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-6371.

**SUPPLEMENTARY INFORMATION:** FDA is announcing the availability of a draft guidance for industry entitled "Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis." This draft guidance is being issued in response to information submitted to the agency regarding the development of osteosarcomas in two strains of rats and one strain of mice following treatment with PTH and related peptides from weaning to 18 months. Given the uncertain clinical relevance of the findings in rodents, and in an effort to improve the benefit to risk ratio of PTH when used in studies of the prevention and/or treatment of osteoporosis, the draft guidance recommends that special consideration be given to the design and conduct of clinical trials evaluating the safety and effectiveness of PTH. These special considerations relate to inclusion and exclusion criteria, patient followup, and patient informed consent.

This draft guidance is being issued consistent with FDA's good guidance practices (62 FR 8961, February 27, 1997). The draft guidance represents the agency's current thinking on the development of parathyroid hormone in the prevention and treatment of osteoporosis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: June 6, 2000.

**Margaret M. Dotzel,**

*Associate Commissioner for Policy.*

[FR Doc. 00-14986 Filed 6-13-00; 8:45 am]

BILLING CODE 4160-01-F

# Guidance for Industry

## Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Eric Colman at 301-827-6371.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**May 2000**

# Guidance for Industry

## Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

***DRAFT GUIDANCE***

*Additional copies of this Draft Guidance are availabile from:*

*Office of Training and Communications*
*Division of Communications Management*
*Drug Information Branch, HFD-210*
*Center for Drug Evaluation and Research*
*5600 Fishers Lane*
*Rockville, MD 20857*
*(Tel) 301-827-4573*
*Internet: http://www.fda.gov/cder/guidance/index.htm*

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**May 2000**

# Table of Contents

*Draft – Not for Implementation*

# Guidance for Industry[1]

## Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis

*If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:*

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

## I. INTRODUCTION

This guidance document provides recommendations for sponsors of new drug applications (NDAs) on clinical trials and drug development programs designed to evaluate the safety and effectiveness of parathyroid hormone (PTH) in the prevention and treatment of osteoporosis. This guidance applies to any form of PTH, including all analogs and related drug substances (e.g., PTHrP).

## II. BACKGROUND

In preclinical studies previously submitted to the Agency, two strains of rats and one strain of mice developed osteosarcomas when given PTH and related peptides from weaning to 18 months of age. Osteosarcomas occur very rarely in mice and rats and were not observed in the control animals in these studies. Many of the tumors were discovered by direct palpation and were often metastatic at the time of discovery, suggesting that they had been present for a long time. Since rodent life expectancy is about 2 years, the animals in these studies were exposed to PTH for most of their life spans. In some cases, tumors occurred in animals at exposures (AUC) equivalent to those commonly used in clinical studies of PTH in the treatment and/or prevention of osteoporosis.

The clinical relevance of these animal findings is not currently known. This guidance was developed by FDA to clarify the Agency's current thinking regarding the impact of these preclinical findings on drug development programs for PTH for the treatment and/or prevention of osteoporosis.

[1] This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the use of parathyroid hormone in the prevention and treatment of osteoporosis. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

## III. PRECLINICAL STUDIES

As a result of the concern about carcinogenicity discussed above, studies to evaluate carcinogenic potential should generally be done for PTH and related peptides. These studies may entail unique design features; therefore, considerations to address these concerns should be discussed with the review staff in the Division of Metabolic and Endocrine Drug Products prior to initiation.

## IV. CLINICAL STUDIES

Given the uncertain clinical relevance of the findings in rodents, and in an effort to improve the benefit to risk ratio of PTH, it is strongly recommended that participation in clinical studies be limited to adults with severe osteoporosis who have completed bone maturation. For the purposes of this recommendation, *severe osteoporosis* is defined as a lumbar spine or hip T-score of <-2.5 and the presence of at least one clinically manifest, radiographically documented osteoporotic fracture at baseline prior to PTH treatment.

Persons with known Paget's disease of the bone or with otherwise unexplained elevations of plasma alkaline phosphatase (above the upper limit of normal for the laboratory) should be excluded because of the known association between Paget's disease and osteosarcoma.

### A. Patient Follow Up

Any case of osteosarcoma (or other bone tumor) that develops in a study participant receiving PTH or with previous exposure to PTH should be immediately reported to the drug sponsor and the FDA.

In order to improve the ability to conduct long-term follow-up of patients treated with PTH in clinical trials, sponsors are encouraged to collect unique identifiers (e.g., name, Social Security number) for those study participants who provide their consent, when consistent with local regulations and statutes.

### B. Patient Informed Consent Form

Sponsors should include information in the informed consent form about the occurrence of osteosarcomas in rodents and are requested to submit these consent forms to FDA's Division of Metabolic and Endocrine Drug Products for review.

Washington
Hospital Center

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